



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US95/07117 <b>(22) International Filing Date:</b> 15 June 1995 (15.06.95) <b>(30) Priority Data:</b> 08/261,785      20 June 1994 (20.06.94)      US <b>(71) Applicant:</b> SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). <b>(72) Inventor:</b> VACCARO, Wayne; 1706 Westover Road, Yardley, PA 19067 (US). <b>(74) Agents:</b> MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		<b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS <b>(57) Abstract</b> <p>Substituted azetidinone hypocholesterolemic agents of formula (I) or a pharmaceutically acceptable salt thereof, wherein: Ar<sup>1</sup> is aryl or R<sup>3</sup>-aryl; Ar<sup>2</sup> is aryl or R<sup>4</sup>-aryl; R<sup>1</sup> is selected from the group consisting of -(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 2-6; -(CH<sub>2</sub>)<sub>e</sub>-Z-(CH<sub>2</sub>)<sub>r</sub>-, wherein Z is -O-, -C(O)-, phenylene, -NR<sup>10</sup>- or -S(O)<sub>0-2</sub>-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6; -(C<sub>2</sub>-C<sub>6</sub> alkenylene)-; and -(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; R<sup>2</sup> is -(lower alkylene)-COR<sup>5</sup> or -(CH=CH)-COR<sup>5</sup>; R<sup>3</sup> and R<sup>4</sup> are independently 1-3 substituents selected from lower alkyl, -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>6</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>R<sup>9</sup>, -COOR<sup>6</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, S(O)<sub>0-2</sub>R<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>, -(lower alkylene)-COOR<sup>6</sup>, -CH=CH-COOR<sup>6</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub> and halogen; R<sup>5</sup> is -OR or -NRR<sup>12</sup>; R, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>12</sup> are independently selected from hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; R<sup>9</sup> is lower alkyl, aryl or aryl-substituted lower alkyl; and R<sup>10</sup> is hydrogen, lower alkyl, aryl lower alkyl or -C(O)R<sup>6</sup>; are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, and pharmaceutical compositions containing them.</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

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10                   **SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS**  
                      **HYPOCHOLESTEROLEMIC AGENTS**

**BACKGROUND OF THE INVENTION**

                      The present invention relates to substituted azetidinones  
useful as hypocholesterolemic agents in the treatment and prevention of  
15    atherosclerosis, and to the combination of a substituted azetidinone of this  
invention and a cholesterol biosynthesis inhibitor for the treatment and  
prevention of atherosclerosis.

                      Atherosclerotic coronary heart disease (CHD) represents the  
major cause for death and cardiovascular morbidity in the western world.  
20    Risk factors for atherosclerotic coronary heart disease include  
hypertension, diabetes mellitus, family history, male gender, cigarette  
smoke and serum cholesterol. A total cholesterol level in excess of 225-  
250 mg/dl is associated with significant elevation of risk of CHD.

                      Cholesteryl esters are a major component of atherosclerotic  
25    lesions and the major storage form of cholesterol in arterial wall cells.  
Formation of cholesteryl esters is also a key step in the intestinal  
absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester  
formation and reduction of serum cholesterol is likely to inhibit the  
progression of atherosclerotic lesion formation, decrease the  
30    accumulation of cholesteryl esters in the arterial wall, and block the  
intestinal absorption of dietary cholesterol.

                      A few azetidinones have been reported as being useful in  
lowering cholesterol and/or in inhibiting the formation of cholesterol-  
containing lesions in mammalian arterial walls. U.S. 4,983,597 discloses  
35    N-sulfonyl-2-azetidinones as anticholesterolemic agents and Ram, et al.,  
in Indian J. Chem., Sect. B, 29B, 12 (1990), p. 1134-7, disclose ethyl 4-(2-  
oxoazetidin-4-yl)phenoxy-alkanoates as hypolipidemic agents. European  
Patent Publication 264,231 discloses 1-substituted-4-phenyl-3-(2-oxo-  
alkylidene)-2-azetidinones as blood platelet aggregation inhibitors.

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European Patent 199,630 and European Patent Application 337,549 disclose elastase inhibitory substituted azetidinones said to be useful in treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.

5 WO93/02048, published February 4, 1993, discloses substituted  $\beta$ -lactams useful as hypocholesterolemic agents.

The regulation of whole-body cholesterol homeostasis in humans and animals involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the  
10 catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density  
15 lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

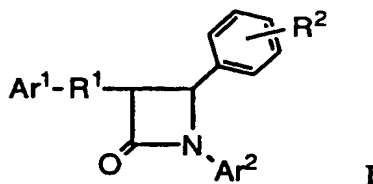
When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The  
20 consequence of this action is decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (EC1.1.1.34) inhibitors  
25 has been shown to be an effective way to reduce plasma cholesterol (Witzum, *Circulation*, 80, 5 (1989), p. 1101-1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in  
30 human hyperlipidemic patients than either agent in monotherapy (Illingworth, *Drugs*, 36 (Suppl. 3) (1988), p. 63-71).

#### SUMMARY OF THE INVENTION

35 Novel hypocholesterolemic compounds of the present invention are represented by the formula I

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or a pharmaceutically acceptable salt thereof, wherein:

Ar<sup>1</sup> is aryl or R<sup>3</sup>-substituted aryl;

Ar<sup>2</sup> is aryl or R<sup>4</sup>-substituted aryl;

5 R<sup>1</sup> is selected from the group consisting of

-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 2, 3, 4, 5 or 6;

-(CH<sub>2</sub>)<sub>e</sub>-Z-(CH<sub>2</sub>)<sub>r</sub>-, wherein Z is -O-, -C(O)-, phenylene, -NR<sup>10</sup>- or -S(O)<sub>0-2</sub>-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-; and

10 -(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R<sup>2</sup> is -(lower alkylene)-COR<sup>5</sup> or -(CH=CH)-COR<sup>5</sup>;

15 R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of lower alkyl, -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>6</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>R<sup>9</sup>, -COOR<sup>6</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, S(O)<sub>0-2</sub>R<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>, -(lower alkylene)-COOR<sup>6</sup>, -CH=CH-COOR<sup>6</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub> and halogen;

20 R<sup>5</sup> is -OR or -NRR<sup>12</sup>, wherein R and R<sup>12</sup> are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

25 R<sup>9</sup> is lower alkyl, aryl or aryl-substituted lower alkyl; and

R<sup>10</sup> is hydrogen, lower alkyl, aryl lower alkyl or -C(O)R<sup>6</sup>.

30 Preferred are compounds of formula I wherein Ar<sup>1</sup> is phenyl or R<sup>3</sup>-substituted phenyl, especially (4-R<sup>3</sup>)-substituted phenyl. Also preferred are compounds of formula I wherein Ar<sup>2</sup> is phenyl or R<sup>4</sup>-substituted phenyl, especially (4-R<sup>4</sup>)-substituted phenyl.

R<sup>3</sup>, when present, is preferably a halogen. R<sup>4</sup>, when present, is preferably halogen or -OR<sup>6</sup>, wherein R<sup>6</sup> is lower alkyl or

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hydrogen. Especially preferred are compounds wherein Ar<sup>2</sup> is 4-fluorophenyl.

R<sup>1</sup> is preferably -(CH<sub>2</sub>)<sub>q</sub>- or -(CH<sub>2</sub>)<sub>e</sub>-Z-(CH<sub>2</sub>)<sub>r</sub>, wherein referred values for q are 2 and 3; Z is preferably -O-; e is preferably 0; and r is preferably 2.

R<sup>2</sup> is preferably in the para-position. When R<sup>2</sup> is -(lower alkylene)-COOR<sup>5</sup>, the lower alkylene portion is preferably methylene or ethylene. R<sup>5</sup> is preferably lower alkyl, especially methyl, or hydrogen.

Another group of preferred compounds is that wherein Ar<sup>1</sup> is phenyl or R<sup>3</sup>-substituted phenyl, especially (4-R<sup>3</sup>)-substituted phenyl, Ar<sup>2</sup> is phenyl or R<sup>4</sup>-substituted phenyl, especially (4-R<sup>4</sup>)-substituted phenyl, and R<sup>1</sup> is -(CH<sub>2</sub>)<sub>q</sub>- or -(CH<sub>2</sub>)<sub>e</sub>-Z-(CH<sub>2</sub>)<sub>r</sub>, wherein Z is -O-.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a substituted azetidinone cholesterol

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absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

5 **DETAILED DESCRIPTION:**

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms. Similarly, "lower alkylene" means a divalent alkyl chain, straight or branched, of 1 to 6 carbon atoms, and "cycloalkylene" means a divalent cycloalkyl group.

10 "Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl. "Phenylene" means a divalent phenyl group.

"Halogeno" refers to fluorine, chlorine, bromine or iodine atoms.

Compounds of the invention have at least one asymmetric  
15 carbon atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating  
20 isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological  
25 activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic,  
30 ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium  
35 bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

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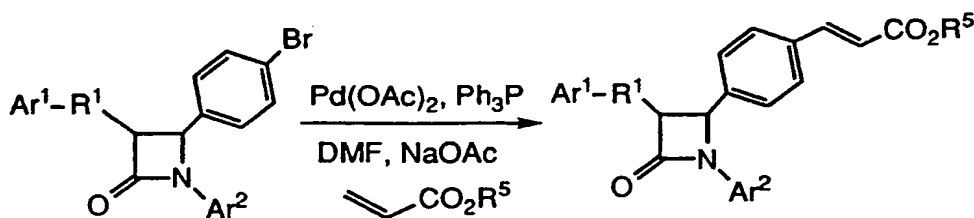
Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases.

- 5 Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

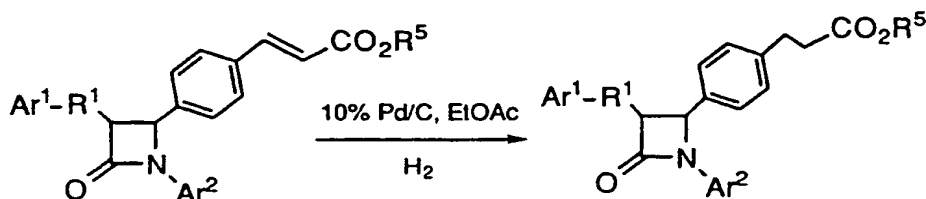
- Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxymethyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

- Compounds of formula I can be prepared by known methods, for example those described in WO93/02048 cited above. Following are general schematic representations of typical procedures; the examples below provide more detailed descriptions. Most of the abbreviations are defined in the examples below; those that are not include Pd(OAc)<sub>2</sub> (palladium diacetate); Ph<sub>3</sub>P (triphenylphosphine); Tf<sub>2</sub>O (triflic anhydride).

Method A:

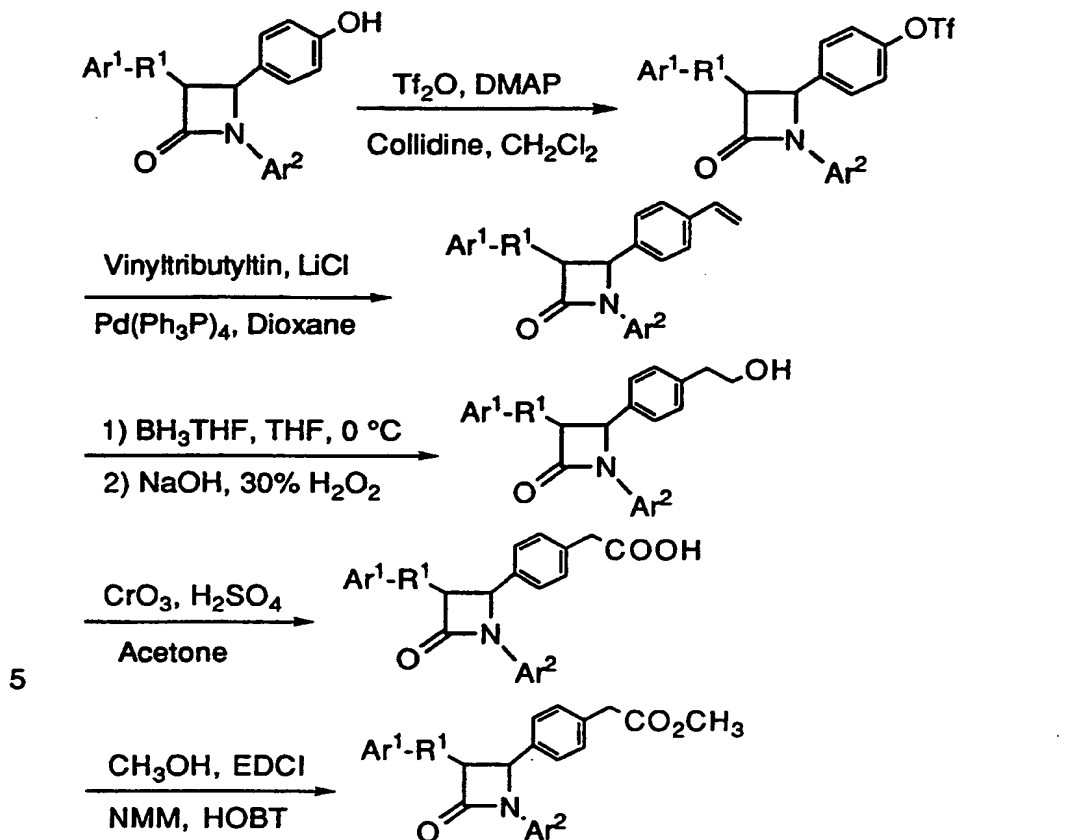


Method B:

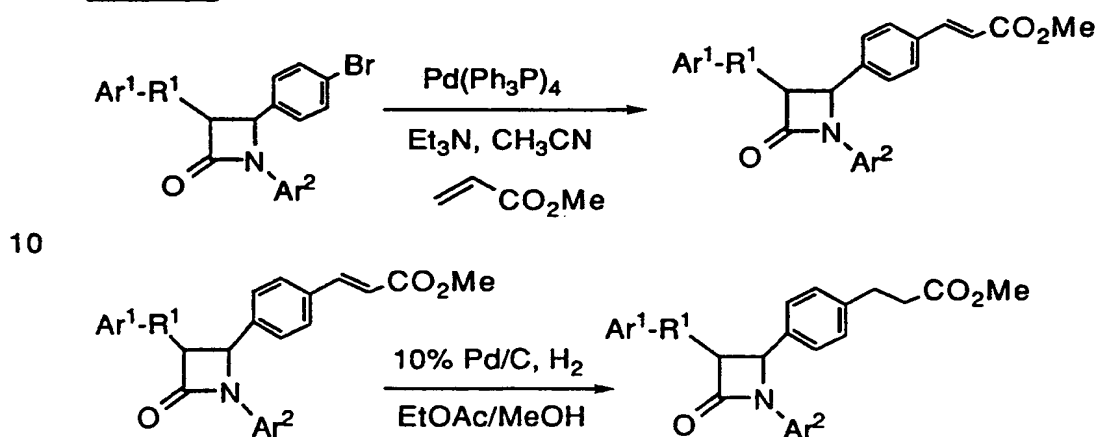




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Method C:

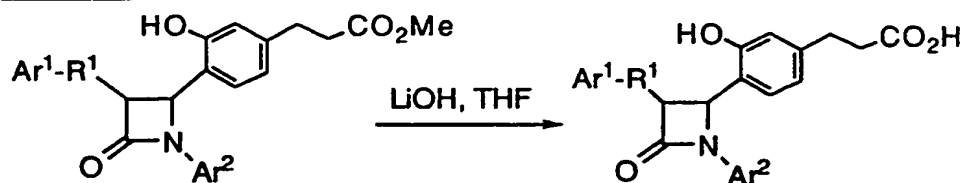
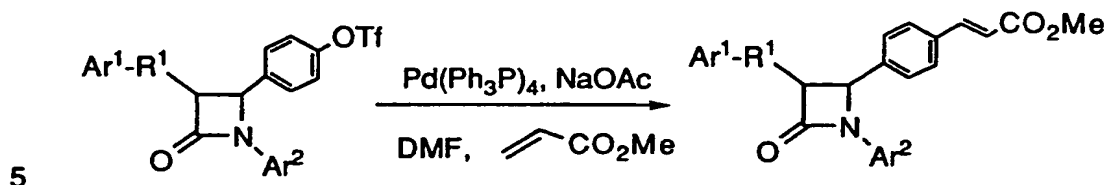
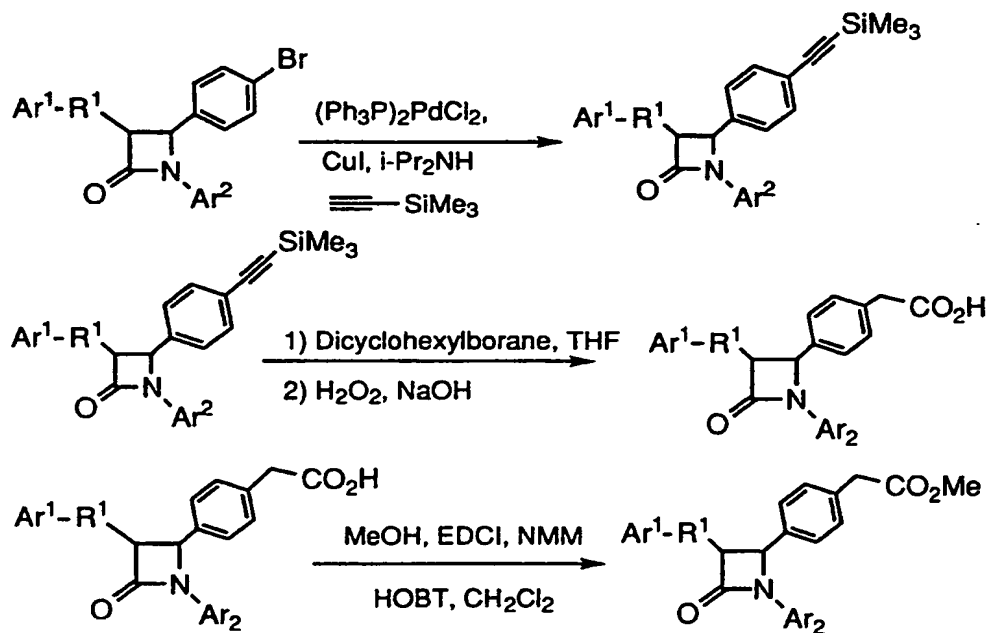
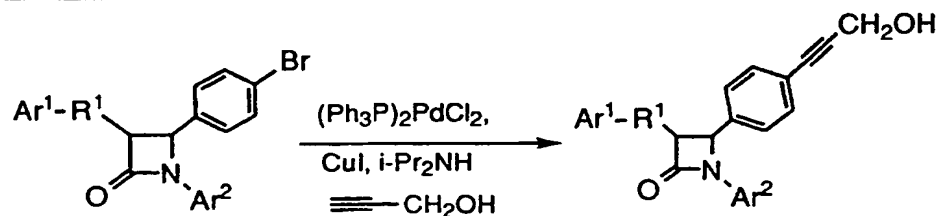
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Method D:

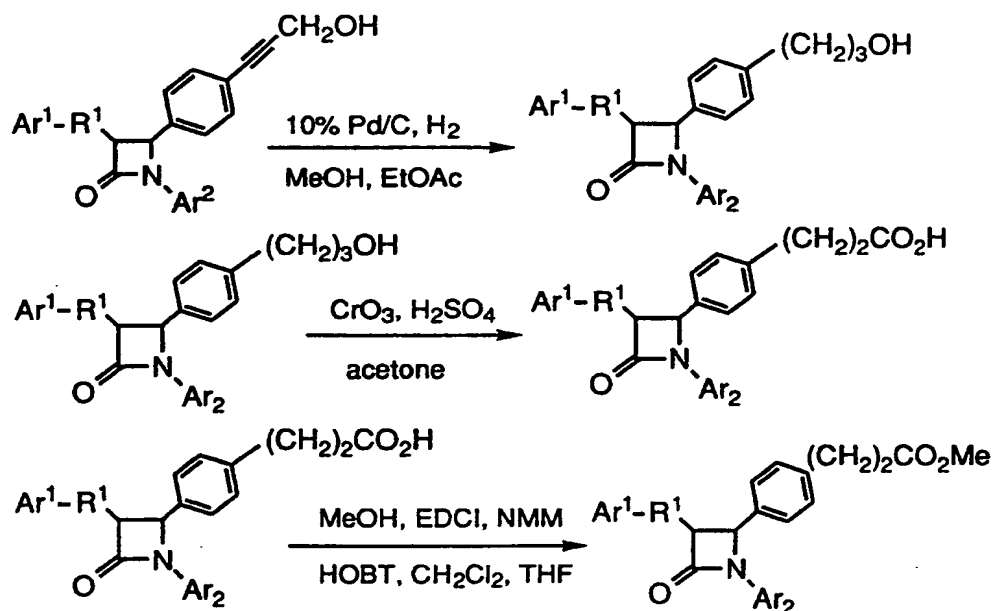
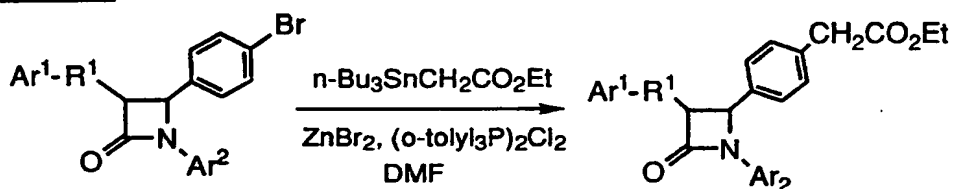
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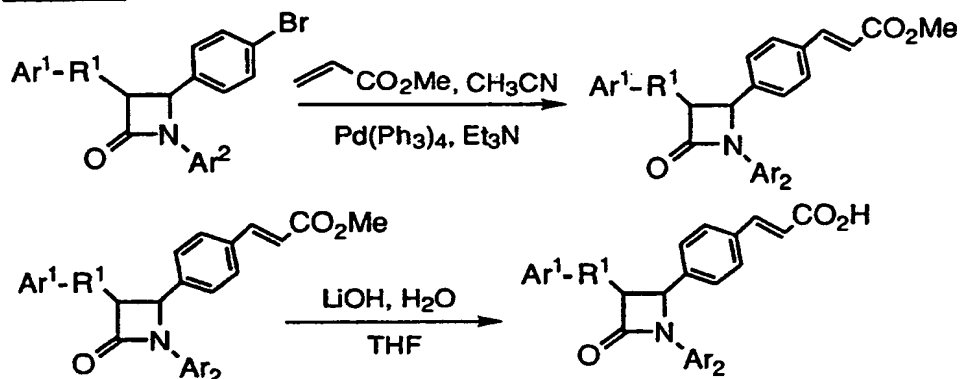
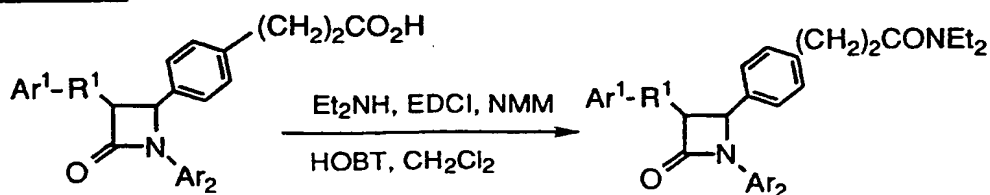
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Method E:Method F:Method G:10 Method H:

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Method I:

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Method J:Method K:

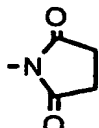
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Starting compounds for the above reactions are all either commercially available or well known in the art and can be prepared via known methods.

- 5 Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 1 shows some typical protecting groups:

Table 1

Group to be Protected	Group to be Protected and Protecting Group
-COOH	-COOalkyl, -COObenzyl, -COOphenyl
>NH	$\begin{array}{l} \text{>NCOalkyl, >NCObenzyl, >NCOphenyl} \\ \text{>NCH}_2\text{OCH}_2\text{CH}_2\text{Si(CH}_3)_3 \quad \text{>NC(O)OC(CH}_3)_3, \\ \text{>N-benzyl, >NSi(CH}_3)_3, \quad \text{>N} \begin{array}{c} \text{CH}_3 \\   \\ \text{Si-C(CH}_3)_3 \\   \\ \text{CH}_3 \end{array} \end{array}$
-NH <sub>2</sub>	
-OH	$\begin{array}{l} \text{-OCH}_3, \text{-OCH}_2\text{OCH}_3, \text{-OSi} \begin{array}{c} \text{CH}_3 \\   \\ \text{C(CH}_3)_3 \end{array} \\ \text{-OSi(CH}_3)_3, \text{ or -OCH}_2\text{phenyl} \end{array}$

10

- We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

- 20 The in vivo activity of the compounds of formula I can be determined by the following procedure:

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In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures (Schnitzer-Polokoff, R., et al, *Comp. Biochem. Physiol.*, 99A, 4 (1991), p. 665-670) and data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesteremic dose of a compound of formula I is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

For the combinations of this invention wherein the hydroxy substituted azetidinone is administered in combination with a cholesterol

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biosynthesis inhibitor, the typical daily dose of the cholesterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divided dosages, usually once or twice a day: for example, for HMG CoA reductase inhibitors, about 10 to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 2000 mg per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a substituted azetidinone cholesterol absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

Following are examples of preparing compounds of formula I. The stereochemistry listed is relative stereochemistry unless otherwise noted. The terms cis and trans refer to the relative orientations at the azetidinone 3- and 4-positions unless otherwise indicated.

#### Example 1

Methyl 4-[1-(4-fluorophenyl)-4-oxo-3-(2-(4-fluorophenoxy)-ethyl)-2-azetidinyl]benzoate

Reflux a solution of 4-formyl methylbenzoate (3.0 g, 18.3 mmol) and 4-fluoroaniline (2.0 g, 18.3 mmol) in toluene (200 mL)

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overnight with azeotropic removal of water via a Dean-Stark trap, monitoring conversion to the corresponding imine by  $^1\text{H}$  NMR of the crude mixture. Remove the Dean-Stark trap and add n-tributylamine (13.0 mL, 54.8 mmol). Add 4-fluorophenoxybutyryl chloride (27.4 mL, 27.4 mmol, 5 1M in toluene) slowly and reflux overnight, monitoring consumption of the imine by  $^1\text{H}$  NMR. Cool the mixture to room temperature, quench with 1M HCl and stir for ~30 min. Dilute the resulting solution with ethyl acetate (EtOAc), wash with 1M HCl, water and brine, dry over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrate to an amber oil. To reduce unreacted starting aldehyde, 10 redissolve the oil in 50%  $\text{CH}_3\text{OH}$ /tetrahydrofuran (THF) (100 mL) and add  $\text{NaBH}_4$  (1.22 g, 32 mmol). After gas evolution ceases (~15 min), quench the reaction with 1M HCl, dilute with EtOAc, wash with 1M HCl, water and brine, dry over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrate onto enough silica gel to obtain a free flowing powder. Load this powder onto a chromatography 15 column prepacked with 20% EtOAc/hexanes and silica. Elute with 20% EtOAc/hexanes to obtain 2.48 g (31%) of the title compound as an 8/1 trans/cis mixture. Purify by HPLC (silica gel, 15% EtOAc/hexanes) to obtain pure cis and trans diastereomers.

In a similar manner, prepare the following compound:

20 1A: Trans 1-(4-methoxyphenyl)-3-(3-phenylpropyl)-4-(4-bromophenyl)-2-azetidinone.

### Example 2

25 Trans Methyl 3-[4-[1-(4-Methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidinyl]phenyl]-2-propenoate

Add  $\text{Pd}(\text{OAc})_2$  (0.036 g, 0.16 mol) and triphenylphosphine ( $\text{Ph}_3\text{P}$ ) (0.097 g, 0.32 mmol) to anhydrous dimethylformamide (DMF) (3 mL) under  $\text{N}_2$ . Stir the mixture at room temperature until homogenous (5 min) and then add to a mixture of the product of Example 1A (3.6 g, 8.8 mmol), sodium acetate (0.72 g, 8.8 mmol), methyl acrylate (0.79 mL, 8.8 mmol) and DMF (10 mL) under  $\text{N}_2$ . Heat the resulting mixture to 130  $^\circ\text{C}$  overnight. Cool the reaction mixture to room temperature, and partition 30 between ether and water. Wash the ether layer with water (5X) and brine, dry over  $\text{Na}_2\text{SO}_4$  and concentrate to an oil. Chromatograph on silica gel (25% EtOAc/hexanes) to obtain 1.27 g (35%) of the title compound as a colorless oil. MS (EI): 455( $\text{M}^+$ , 17), 306(54), 215(45), 188(41), 149(100), 35 91(68).

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**Example 3****Trans methyl 3-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-propanoate**

- Dissolve the product of Example 2 (0.35 g, 0.77 mmol) in EtOAc (6 mL) and purge with N<sub>2</sub>. Add 10% Pd/C (0.082 g), purge the resulting suspension with H<sub>2</sub> and stir under a balloon of H<sub>2</sub> for 3 h. Filter the mixture through celite, wash the filter cake with EtOAc and concentrate the filtrate to obtain 0.35 g (100%) of the title compound as a clear oil. MS (EI): 455(M<sup>+</sup>, 13), 308(31), 217(78), 185(25), 149(52), 129(100).
- 10 In a similar manner, prepare:  
3A: **Trans methyl 3-[(3R, 2S)-4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-propanoate**: (prepared from trans methyl 3-[(3R, 2S)-4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-2-propanoate, prepared as described in Example 9.
- 15 M.p. 91-92°C. HRMS calc'd for C<sub>29</sub>H<sub>31</sub>NO<sub>4</sub>: 457.2252; found 457.2274. (EI): 457(M<sup>+</sup>, 100), 308(52), 252(59), 160(46).

**Example 4****Trans Methyl 2-[4-[1-(4-Methoxyphenyl)-4-oxo-3(R)-(3-phenylpropyl)-2(S)-azetidiny]phenyl]ethanoate**

- 20 Step 1: (5S)-1-(5-Phenyl-1-oxo-pentanyl)-5-phenyloxalozidinone:  
Slowly add 5-phenylvaleryl chloride (15.4 g, 78.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) via cannula to a 0 °C solution of (5S)-5-phenyl-oxazolidinone (10.6 g, 65.1 mmol), triethylamine (Et<sub>3</sub>N) (21.8 mL, 156.2 mmol) and dimethylaminopyridine (DMAP) (0.56 g, 4.56 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (160 mL).  
25 After addition, allow the mixture to warm to room temperature overnight. Add water and stir the mixture for 30 min.; wash with 1M HCl, water, NaHCO<sub>3</sub> (sat'd), water and brine, dry over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrate to obtain the title compound of Step 1 as an amber oil, 24.2g  
30 (~100%).  
Step 2:  
Add TiCl<sub>4</sub> (38 mL, 38 mmol, 1M in CH<sub>2</sub>Cl<sub>2</sub>) dropwise to a -40 °C solution of (5S)-1-(5-phenyl-1-oxo-pentanyl)-5-phenyl-oxalozidinone (12.3 g, 38.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (125 mL) over 10 min. Stir for an additional  
35 10 min., then add Hunig's base (13.2 mL, 76 mmol) over 8 min. while maintaining the temperature at -40 °C. Stir the resulting solution for 30 min. Add N-(4-benzyloxybenzylidene)-4-methoxyaniline (21.6 g, 68.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (450 mL) via cannula over 40 min., again maintaining



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the reaction temperature at -50 to -40 °C. Stir the mixture for 3 h and allow to warm to -20 °C. Quench the reaction by slowly adding acetic acid (20 ml) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), stir the mixture for 30 min. and then pour into a 0 °C solution of 2N H<sub>2</sub>SO<sub>4</sub> (500 mL) and EtOAc (500 mL) and stir rapidly for 1h. Filter the resulting mixture, extract the filtrate with EtOAc, wash the combined extracts with NaHCO<sub>3</sub> (sat'd) and brine, dry over Na<sub>2</sub>SO<sub>4</sub> and concentrate to a beige solid (20 g). Recrystallize from EtOAc to obtain 8.08 g (34%) of an off white solid.

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- Step 3: Trans (3R,4S)- 1-(-methoxyphenyl)-3-(3-phenylpropyl)-4-(4-benxyloxyphenyl)-2-azetidinone:

Add N,O-bis(trimethylsilyl)acetamide (4.6 ml, 18.8 mmol) to a 90 °C solution of the product of Step 2 (8.03 g, 12.5 mmol) in toluene (100 mL) and stir for 1h. Add tetrabutylammonium fluoride (0.16 g, 0.63 mmol) and stir the mixture at 90 °C for an additional hour. Cool the mixture to room temperature and quench the reaction with CH<sub>3</sub>OH (10 mL). Dilute the mixture with EtOAc, wash with 1M HCl, NaHCO<sub>3</sub> (sat'd), water and brine, then concentrate to a white solid. Purify the solid further by chromatography on silica gel (30% EtOAc/hexane) to obtain 5.46 g (91%) of the title compound of Step 3 as a white solid.

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- Step 4: Trans (3R,4S)- 1-(-methoxyphenyl)-3-(3-phenylpropyl)-4-(4-hydroxyphenyl)-2-azetidinone:

Hydrogenate a suspension of the product of Step 3 in 50% CH<sub>3</sub>OH/EtOAc (100 mL) with 10% Pd/C (0.42 g) on a Parr apparatus at 60 psi overnight. Filter the reaction mixture through celite and concentrate the filtrate to provide 5 g of a foam. Purify the foam by silica gel chromatography (40-100% EtOAc/hexane) to provide 4.05 g (92%) of the title compound of Step 4 as a white solid.

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- Step 5: Trans (3R,4S)- 1-(-methoxyphenyl)-3-(3-phenylpropyl)-4-(4-trifluoromethanesulfonyl)phenyl)-2-azetidinone:

Add triflic anhydride (0.57 mL, 3.4 mmol) to a 0 °C solution of the product of Step 4 (1.2 g, 3.1 mmol), DMAP (0.1 g) and 2,4,6-collidine (0.44 mL, 3.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL). After 30 min., quench the reaction with water and extract with EtOAc. Combine the extracts, wash with NH<sub>4</sub>Cl (sat'd), NaHCO<sub>3</sub> (sat'd), water and brine, dry over Na<sub>2</sub>SO<sub>4</sub> and concentrate to obtain 1.7 g (100%) of the title compound of Step 5 as an oil.

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- Step 6: Trans (3R,4S)-1-(4-Methoxyphenyl)- 3-(3-phenylpropyl)-4-(4-vinylphenyl)-2-azetidinone:

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- Dissolve the product of Step 5 (1.22g, 2.35 mmol) in dioxane (30 mL), add LiCl (0.30 g, 7.04 mmol) and palladium tetrakis(triphenylphosphine) ( $\text{Pd}(\text{Ph}_3\text{P})_4$ ) (0.28 g, 0.24 mmol). Add vinyltributyltin (0.83 ml, 2.82 mmol) and heat the mixture to 90 °C, monitoring the reaction by TLC (25% EtOAc/hexanes). Cool the mixture to room temp., treat with 2.5 M KF (30 mL) and stir the mixture overnight. Filter the resulting solution, dilute with EtOAc, wash with water and brine, dry over  $\text{Na}_2\text{SO}_4$  and concentrate to a yellow oil. Chromatograph on silica gel (20% EtOAc/hexane) to obtain 0.447 g (50%) of the title compound of Step 6 as an oil.
- 5 Step 7: Trans Methyl 4-[1-(4-Methoxyphenyl)-4-oxo-3(R)-(3-phenylpropyl)-2(S)-azetidiny]phenyl-2-ethanol:
- Add borane tetrahydrofuran complex (3.4 mL, 3.4 mmol) to a 0 °C solution of the product of Step 6 (0.45 g, 1.12 mmol) in THF (15 mL) and allow the mixture to warm to room temperature overnight. Add 2N NaOH (1.7 ml) followed by 30%  $\text{H}_2\text{O}_2$  (1.2 mL) and stir the mixture for 3h. Quench the mixture by adding 0.8M  $\text{Na}_2\text{SO}_3$  solution (2 mL). Extract the mixture ether, wash the etheral extracts with water and brine, dry over  $\text{Na}_2\text{SO}_4$  and concetrate. Chromatograph on silica (30% EtOAc/hexanes) to obtain 0.18 g (41%) of the title compound of Step 7 as an oil.
- 15 Step 8: Trans Methyl 2-[4-[1-(4-Methoxyphenyl)-4-oxo-3(R)-(3-phenylpropyl)-2(S)-azetidiny]phenyl]-acetic acid:
- Add Jones Reagent (0.4 ml, prepared by dissolving 6.7 g chromic acid in concentrated  $\text{H}_2\text{SO}_4$  and diluting with distilled water to 50 mL) to a solution of the product of Step 7 (0.15 g, 0.36 mmol) in acetone (4 mL), monitoring the reaction by TLC (5% MeOH/ $\text{CH}_2\text{Cl}_2$ ). Add  $\text{CH}_3\text{OH}$  (2 mL) and stir the mixture for 30 min. Concentrate the mixture, partition the residue between water and  $\text{CH}_2\text{Cl}_2$ , and extract with  $\text{CH}_2\text{Cl}_2$ . Combine the extracts, wash with  $\text{Na}_2\text{SO}_3$  (sat'd), water and brine, dry over  $\text{Na}_2\text{SO}_4$  and concentrate to obtain 0.144 g (93%) of the title compound of Step 8 as a yellow foam.
- 20 Step 9:
- Using a well known procedure, add 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) to a solution of the product of Step 8, ethanol, hydroxybenzotriazole (HOBT) and N-methylmorpholine (NMM) in  $\text{CH}_2\text{Cl}_2$  and stir the mixture overnight. Dilute the resulting reaction mixture with  $\text{CH}_2\text{Cl}_2$ , wash with 1M HCl, water and brine, dry over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrate to an oil. Chromatograph the residue on silica (3%  $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) to obtain 0.090 g (61%) of the title
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compound. HRMS calc'd for  $C_{28}H_{29}NO_4$ : 443.2097; found 443.2093. MS (CI): 444 ( $M+1$ , 100).

### Example 5

5 Trans methyl 3-[3-benzyloxy-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]]phenyl]propenoate

Combine trans-1-(4-fluorophenyl)-3-(3-phenylpropyl)-4-(4-bromo-2-benzyloxyphenyl)-2-azetidinone (0.55 g, 1.0 mmol) (prepared according to the procedure of Example 1), triethylamine (0.28 mL, 2.0 mmol), methyl acrylate (0.18 mL, 2.0 mmol) and  $Pd(Ph_3P)_4$  (0.058 g, 0.05 mmol) in 10  $CH_3CN$  (2 mL) and heat to 80 °C over night. Monitor the reaction by TLC (25% EtOAc/hexane); add methyl acrylate (0.18 mL, 2.0 mmol) and  $Pd(Ph_3P)_4$  (0.058 g, 0.05 mmol) and heat the mixture for an additional 20 h. at 80 °C. Cool the reaction mixture to room temperature, dilute with EtOAc, wash with 0.1 N HCl, water and brine, dry over  $Na_2SO_4$  and 15 concentrate. Chromatograph the residue on silica (20% EtOAc/hexane) to obtain 0.27 g (48%) of the title compound as a yellow solid.

5A: In a similar manner, prepare trans methyl 3-[4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]]phenyl]propenoate.

### Example 6

20 trans methyl 3-[3-hydroxy-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]]phenyl]propionate

Dissolve the product of Example 5 (0.266 g, 0.48 mmol) in EtOAc (16 mL), dilute with  $CH_3OH$  (20 mL) and purge with  $N_2$ . Add 20% Pd/C (0.05 g), purge the mixture with  $H_2$  and then stir under a balloon of 25  $H_2$  overnight. Filter the reaction mixture through celite. Wash the filter cake with EtOAc and concentrate the filtrate to give 0.156 g of the title compound as a colorless oil. HRMS calc'd for  $C_{28}H_{28}NO_4$ :  $M+H$  462.2081; found 462.2070. MS (CI): 462 ( $M+1$ , 37), 351(17), 293(41), 138(100).

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### Example 7

trans 3-[3-hydroxy-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]]phenyl]propionic acid

Dissolve the product of Example 6 (0.066g, 0.14 mmol) in THF (3 mL), add LiOH (0.04 g, 0.86 mmol) and stir the mixture at room 35 temperature overnight. Acidify the solution to pH 3 with 1M HCl, dilute with EtOAc, wash with water and brine, dry over  $Na_2SO_4$  and concentrate to give 0.061 g, (91%) of the title compound as an oil. HRMS calc'd for  $C_{27}H_{26}NO_4$ :  $M+H$  448.1924; found 448.1911. (FAB): 444 ( $M+1$ , 100).

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**Example 8****Trans Methyl 3-[3-[1-phenyl-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]propenoate**

- 5 **Step 1:** Prepare trans 1-phenyl-3-(3-phenylpropyl)-4-(3-benzyl-oxyphenyl)-2-azetidinone in a manner similar to that described in Example 1.
- Step 2:** Using the procedure of Example 4, Step 4, treat the product of Step 1 to obtain trans 1-phenyl-3-(3-phenylpropyl)-4-(3-hydroxyphenyl)-2-azetidinone.
- 10 **Step 3:** Using the procedure of Example 4, Step 5, treat the product of Step 2 to obtain trans 1-phenyl-3-(3-phenylpropyl)-4-((3-trifluoromethyl-sulfonyl)phenyl)-2-azetidinone.
- Step 4:** Using the procedure of Example 5, treat the product of Step 3 to obtain compound 8-1, trans methyl 3-[3-[1-phenyl-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-2-propenoate.
- 15 **Step 5:** Using the procedure of Example 3, treat the product of Step 4 to obtain the title compound (8-2). HRMS calc'd for C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub>: M<sup>+</sup>H 428.2226; found 428.2235. MS (CI): 428 (M<sup>+</sup>,100).

**Example 9**

- 20 **Trans (3R,2S)-Methyl 3-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenyl-propyl)-2-azetidiny]phenyl]-2-propenoate**
- Heat the product of Example 4, Step 5 (0.51 g, 0.98 mmol), sodium acetate (0.1 g, 1.1 mmol), DMF (6 mL) and methyl acrylate (0.1 mL, 1.1 mmol) to 130 °C. Add Pd(Ph<sub>3</sub>P)<sub>4</sub> (0.1 g, 0.11 mmol) and stir the mixture at 130 °C overnight. Cool the mixture to room temperature, partition between water and ether, and extract with ether. Combine the ethereal extracts, wash with water and brine, dry over Na<sub>2</sub>SO<sub>4</sub> and concentrate. Chromatograph the residue on silica (25% EtOAc/hexanes) to provide 0.18 g (40%) of the title compound as a clear oil. HRMS calc'd for C<sub>29</sub>H<sub>29</sub>NO<sub>4</sub>: 455.2097; found 455.2080. MS (EI): 455 (M<sup>+</sup>,72), 371(40), 306(56), 252(100).
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**Example 10**

- (3S, 2R) trans methyl 4-[1-(4-chlorophenyl)-4-oxo-3-(2-(4-fluoro-phenoxy)ethyl)-2-azetidiny]phenyl-2-propenoate (10A) and**
- 35 **(3R, 2S) trans methyl 4-[1-(4-chlorophenyl)-4-oxo-3-(2-(4-fluoro-phenoxy)ethyl)-2-azetidiny]phenyl-2-propenoate (10B)**
- Add 4-(4-fluorophenoxy)butyl chloride (0.72 g, 3.34 mmol) dropwise to a solution of 4-formyl methylpropenoate 4-chloroaniline imine

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- (0.5 g, 1.67 mmol) and Hunig's base (0.87 mL, 5.0 mmol) in dichloroethane (46 mL) at 80 °C. Reflux the mixture overnight, cool to room temperature, quench with 1M HCl and stir for 15 min. Wash the mixture with NaHCO<sub>3</sub> (sat'd), water and brine, dry over Na<sub>2</sub>SO<sub>4</sub> and concentrate.
- 5 Chromatograph the residue on silica (40% EtOAc/hexane). To remove 4-formyl methylbenzoate contaminant, dissolve the product in 50% CH<sub>3</sub>OH/THF and treat with NaBH<sub>4</sub> (1.5 g). After 30 min, quench with NH<sub>4</sub>Cl (sat'd), wash with NH<sub>4</sub>Cl (sat'd), water and brine, dry over Na<sub>2</sub>SO<sub>4</sub> and concentrate. Chromatograph the residue on silica (35%
- 10 EtOAc/hexanes) to provide 0.57g (33%) of trans methyl 4-[1-(4-chlorophenyl)-4-oxo-3-(2-(4-fluorophenoxy)ethyl)-2-azetidiny]phenyl-2-propenoate. Resolve the diastereomers by chiral HPLC (Chiracel AS column, 30% isopropanol/hexanes, 70 mL/min) to give 0.128 g compound 10A and 0.139 g compound 10B.
- 15 10A: HRMS calc'd for C<sub>27</sub>H<sub>23</sub>NO<sub>4</sub>Cl: 480.1378; found 480.1378. (CI): 480(M<sup>+</sup>, 100), 215(99).
- 10B: HRMS calc'd for C<sub>27</sub>H<sub>23</sub>NO<sub>4</sub>Cl: 480.1378; found 480.1369. (CI): 480(M<sup>+</sup>, 88), 215(100).

**Example 11**

20 Trans 3-[4-[1-(4-Methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]propanoic acid

- Step 1: Hydrolyze the product of Example 2 according to the procedure described in Example 7 to obtain trans 3-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-2-propenoic acid (compound 11-1).
- 25 Step 2: Hydrogenate the product of Step 1 according to the procedure described in Example 3 to obtain the title compound (11-2). HRMS calc'd for C<sub>28</sub>H<sub>31</sub>NO<sub>4</sub>: M+H 444.2175; found 444.2165. (FAB): 444(M+1, 100).

**Example 12**

30 Trans Methyl (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanoate

- Step 1: Trans (3R, 4S)-1-(4-fluorophenyl)-4-(4-((trimethylsilyl)acetylenyl)-phenyl)-3-(3-phenylpropyl)-2-azetidinone:
- Heat a mixture of trans (3R, 4S)-1-(4-fluorophenyl)-4-(4-bromophenyl)-3-(3-phenylpropyl)-2-azetidinone (0.69 g, 1.57 mmol) (prepared from N-(4-bromobenzylidene)-4-fluoroaniline and (5S)-1-(5-phenyl-1-oxopentanyl)-5-phenyloxazolidinone using the procedure described in steps 2 and 3 of Example 4), (trimethylsilyl)acetylene (0.33 mL, 2.36 mmol), bis(triphenylphosphine)palladium (II) chloride ((Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>) (0.055g,
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0.079 mmol) and diisopropylamine (6 mL) to 80 °C. Monitor the reaction by TLC. After 80 min, add additional (trimethylsilyl)acetylene (0.33 mL, 2.36 mmol). After an additional 50 min, cool the mixture to room temperature, filter through celite and wash the filter cake with CH<sub>2</sub>Cl<sub>2</sub>.

- 5 Concentrate the filtrate onto enough silica so that a free flowing powder is obtained. Load the resulting powder onto a chromatography column prepacked with silica and 10% EtOAc/hexane. Elute with 10% EtOAc/hexane to obtain 0.595 g (83%) of the title compound of Step 1 as a light brown solid. MS(FAB): 456 (M<sup>+</sup>, 100), 318(37), 296(35).

- 10 Step 2: Trans (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzeneacetic acid:

Add cyclohexane (1.08 mL, 10.64 mmol) to a 0 °C solution of borane (5.3 mL, 5.3 mmol, 1M in THF). Stir at 0 °C for 1 h. Dropwise add the product of step 1 (0.485 g, 1.07 mmol) in THF (7.5 mL) and keep the mixture at 0 °C overnight (22h). Sequentially add CH<sub>3</sub>OH (0.43 mL), 3N NaOH (1.06 mL) and 30 % H<sub>2</sub>O<sub>2</sub> (1.2 mL) to the 0 °C mixture. Allow the mixture to warm to room temperature and stir for 3 h. Pour the mixture into brine and acidify with 1M HCl. Extract with EtOAc, combine the extracts,

- 15 wash with water and brine, dry over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrate onto enough silica that a free flowing powder is obtained. Load the resulting powder onto a chromatography column prepacked with silica and 5% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>. Elute with 5% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> to obtain the title compound of Step 2, 0.227 g (52%). HRMS calc'd for C<sub>26</sub>H<sub>25</sub>NO<sub>3</sub>F: (M+H) 418.1818; found 418.1820. MS(Cl): 418 (M+H, 18), 235(29), 145(55), 83(100).

20 Step 3: Using a procedure similar to that of Example 4, step 9, treat the product of step 3 to obtain the title compound, 0.023 g (25%). HRMS calc'd for C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub>F: (M+H) 446.2131; found 446.2150. MS(Cl): 446 (M+H, 100), 277(13), 138(44).

- 25 **Example 13**

Trans Methyl (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanoate

Step 1: Trans (3R, 4S)-1-(4-fluorophenyl)-4-(4-(3-hydroxy-1-propynyl)-phenyl)-3-(3-phenylpropyl)-2-azetidinone:

- 35 Use a procedure similar to that of Example 12, Step 1, substituting propargyl alcohol (0.20 mL, 3.49 mmol) for (trimethylsilyl)acetylene and refluxing overnight. Filter and chromatograph as in Example 12, Step 1, using a column prepacked with silica and 30% EtOAc/hexane. Elute with

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30% EtOAc/hexane to obtain the title compound of Step 1, 0.73g (75%), as a yellow oil. HRMS calc'd for  $C_{27}H_{25}NO_2F$ : (M+H) 414.1869; found 414.1854. MS(Cl): 414 (M+H, 72), 259(32), 138(100).

Step 2: Trans (3R, 4S)-1-(4-fluorophenyl)-4-(4-(3-hydroxy-1-propyl)-phenyl)-3-(3-phenylpropyl)-2-azetidinone:

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Using the procedure of Example 6, treat the product of Step 1 to obtain 0.42 g (100%) of the title compound of Step 2. MS(Cl): 418 (M+H, 100), 138(55).

Step 3: Trans (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanoic acid:

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Add Jones's Reagent (1.0 mL, prepared as described in Example 4, step 7) to a 0 °C solution of the product of Step 2 in acetone (8 mL). Monitor the reaction by TLC (5%  $CH_3OH/CH_2Cl_2$ ). Upon consumption of starting material, quench the reaction by the addition of  $CH_3OH$  and concentrate in vacuo. Dissolve the residue in water, and adjust to pH 13 with NaOH. Extract the resulting solution with ether, acidify the aqueous layer to pH 3 with HCl (conc.) and extract with EtOAc. Combine the extracts, wash with 10%  $NaHSO_3$ , water and brine, dry over anhydrous  $Na_2SO_4$  and concentrate onto enough silica that a free flowing powder is obtained. Load the resulting powder onto a chromatography column prepacked with silica and 5%  $CH_3OH/CH_2Cl_2$ . Elute with 5-8%  $CH_3OH/CH_2Cl_2$  to obtain 0.243g (53%) of the title compound of Step 3 as a white foam. HRMS calc'd for  $C_{27}H_{27}NO_3F$ : (M+H) 432.1975; found 432.1972. MS(Cl): 432 (M+H, 100).

Step 4: Using a procedure similar to that of Example 4, step 9, but using THF, treat the product of step 3 to obtain the title compound, 0.54 g (57%). HRMS calc'd for  $C_{28}H_{29}NO_3F$ : (M+H) 446.2131; found 446.2150. MS(Cl): 446 (M+H, 100), 277(13), 138(44).

#### Example 14

30 Trans Ethyl (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzene acetate

Dry  $ZnBr_2$  (0.335 g, 1.49 mmol) at 130 °C under vacuum overnight, then cool to room temperature under nitrogen. Add a solution of trans (3R, 4S)-1-(4-fluorophenyl)-4-(4-bromophenyl)-3-(3-phenylpropyl)-2-azetidinone (0.050 g, 1.14 mmol) and ethyl 2-tributyltin acetate (0.56 g, 1.49 mmol) in DMF (3 mL) via cannula under nitrogen. Heat the mixture to 80 °C. Monitor consumption of starting material by TLC (15% EtOAc/hexane) and upon completion, cool to room temperature, filter

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through celite, and wash the filter cake with EtOAc. Add 2.5 M KF (10 mL) to the filtrate, stir for 3h, dilute with EtOAc, wash with water and brine, dry over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrate onto enough silica that a free flowing powder is obtained. Load the resulting powder is loaded onto a chromatography column prepacked with silica and 15% EtOAc/hexane. Elute with 15% EtOAc/hexane to obtain the title compound as a yellow oil, 0.416g (82%). HRMS calc'd for C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub>F: (M+H) 446.2131; found 446.2123. MS(FAB): 446 (M+H, 100), 308(18), 286(24).

**Example 15**

10     Trans (3R, 2S)-3-[4-[1-(4-Fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-E-2-propenoic acid

Step 1: Trans methyl (3R, 2S)-3-[4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-E-2-propenoate:

15     Treat trans (3R, 4S)-1-(4-fluorophenyl)-4-(4-bromophenyl)-3-(3-phenylpropyl)-2-azetidinone methyl acrylate in a manner similar to that described in Example 5 to obtain the title compound of Step 1. HRMS calc'd for C<sub>28</sub>H<sub>27</sub>NO<sub>3</sub>F: (M+H) 444.1975; found 444.1971. MS(CI): 444 (M+H, 100).

20     Step 2: Treat the product of step 1 as described in Example 7, purifying by chromatography on a column prepacked with silica and 0.5% HOAc/2.5% EtOH/97% CH<sub>2</sub>Cl<sub>2</sub>, eluting with the same eluant to obtain the title compound. HRMS calc'd for C<sub>27</sub>H<sub>25</sub>NO<sub>3</sub>F: (M+H) 430.1818; found 430.1810. MS(CI): 430 (M+H, 100), 293(26), 177(74), 138(52).

**Example 16**

25     Trans N,N-Diethyl-(3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanamide

30     Add EDCI (0.058 g, 0.303 mmol) to a mixture of the product of Step 3 of Example 13 (0.092 g, 0.213 mmol), HOBt hydrate (0.035 g, 0.256 mmol), NMM (0.029 mL, 0.277 mmol) and Et<sub>3</sub>N (0.044 mL, 0.427 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL). Stir the resulting mixture overnight until TLC (50% EtOAc/hexane) indicates consumption of starting material. Dilute the mixture with CH<sub>2</sub>Cl<sub>2</sub>, wash with 0.2N HCl, water and brine, dry over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrate onto enough silica such that a free flowing powder is obtained. Load the resulting powder is loaded onto a chromatography column prepacked with silica and 35% EtOAc/hexane. Elute with 35-50% EtOAc/hexane to obtain an oil which is further purified by silica chromatography, eluting with 35-50% EtOAc/hexanes to obtain the title compound, 0.68g (73%), as an oil. MS(CI): 487 (M+, 100).



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350(19), 318(37). HRMS(FAB): calcd. for  $C_{31}H_{36}N_2O_2F(M+1)$ , 487.2761; found 487.2783.

- 5 The following formulations exemplify some of the dosage forms of this invention. In each the term "active compound" designates a compound of formula I.

**EXAMPLE A**

<u>Tablets</u>			
<u>No.</u>	<u>Ingredient</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	<u>3</u>	<u>7</u>
Total		300	700

10 **Method of Manufacture**

- Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

**EXAMPLE B**

<u>Capsules</u>			
<u>No.</u>	<u>Ingredient</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	<u>4</u>	<u>7</u>
Total		250	700

20 **Method of Manufacture**

- Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into

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suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

Using the test procedures described above, the following in vivo data were obtained for representative compounds of formula I. Compounds are referred to by the corresponding example number; data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

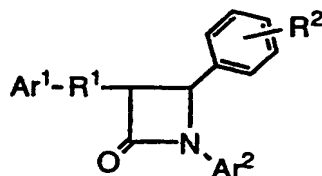
Ex. No.	% Reduction		Dose mg/kg
	Serum Cholesterol	Cholesterol Esters	
1	-28	-76	50
5A	-21	-48	10
16	0	-19	10

For racemic compounds of formula I or active diastereomers or enantiomers of compounds of formula I, compounds administered at dosages of 1-50 mg/kg show a range of -97 to -12% reduction in cholesterol esters, and a -49 to 0% reduction in serum cholesterol. The reduction in cholesterol esters is the more important measure of activity, and active compounds preferably show a range of -30 to -97% reduction in cholesterol esters.

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We claim:

1. A compound represented by the formula



- 5 or a pharmaceutically acceptable salt thereof, wherein:

Ar<sup>1</sup> is aryl or R<sup>3</sup>-substituted aryl;

Ar<sup>2</sup> is aryl or R<sup>4</sup>-substituted aryl;

R<sup>1</sup> is selected from the group consisting of

-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 2, 3, 4, 5 or 6;

10 -(CH<sub>2</sub>)<sub>e</sub>-Z-(CH<sub>2</sub>)<sub>r</sub>-, wherein Z is -O-, -C(O)-, phenylene,

-NR<sup>10</sup>- or -S(O)<sub>0-2</sub>-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-; and

-(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1-5

15 and g is 0-5, provided that the sum of f and g is 1-6;

R<sup>2</sup> is -(lower alkylene)-COR<sup>5</sup> or -(CH=CH)-COR<sup>5</sup>;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of lower alkyl, -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>6</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>,

20 -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>R<sup>9</sup>,

-COOR<sup>6</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, S(O)<sub>0-2</sub>R<sup>9</sup>,

-O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>, -(lower alkylene)-COOR<sup>6</sup>,

-CH=CH-COOR<sup>6</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub> and halogen;

R<sup>5</sup> is -OR or -NRR<sup>12</sup>, wherein R and R<sup>12</sup> are independently

25 selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R<sup>9</sup> is lower alkyl, aryl or aryl-substituted lower alkyl; and

30 R<sup>10</sup> is hydrogen, lower alkyl, aryl lower alkyl or -C(O)R<sup>6</sup>.

2. A compound of claim 1 wherein Ar<sup>1</sup> is phenyl and Ar<sup>2</sup> is phenyl or R<sup>4</sup>-substituted phenyl, wherein R<sup>4</sup> is halogeno or -OR<sup>6</sup>, and wherein R<sup>6</sup> is hydrogen or lower alkyl.

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3. A compound of claim 1 or 2 wherein  $R^1$  is  $-(CH_2)_q-$  or  $-(CH_2)_e-Z-$   $(CH_2)_r$  wherein  $q$  is 2 or 3;  $Z$  is  $-O-$ ;  $e$  is 0; and  $r$  is 2.
- 5 4. A compound of any of claims 1, 2 or 3 wherein  $R^5$  is  $-OR$ , wherein  $R$  is hydrogen or lower alkyl.
5. A compound of claim 1 selected from the group consisting of
  - trans methyl 3-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-2-propenoate;
  - 10 trans methyl 3-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-propanoate;
  - trans methyl 3-[(3S, 2R)-4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]propanoate;
  - 15 trans methyl 2-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]ethanoate;
  - trans methyl 3-[3-[1-phenyl-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]propanoate;
  - trans (3R,4S)-methyl 3-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-2-propenoate;
  - 20 (3S, 2R) trans methyl 4-[1-(4-chlorophenyl)-4-oxo-3-(2-(4-fluorophenoxy)ethyl)-2-azetidiny]phenyl-2-propenoate;
  - (3R, 2S) trans methyl 4-[1-(4-chlorophenyl)-4-oxo-3-(2-(4-fluorophenoxy)ethyl)-2-azetidiny]phenyl-2-propenoate;
  - 25 trans 3-[4-[1-(4-methoxyphenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]propanoic acid;
  - trans methyl 3-[4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]propenoate;
  - trans (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzeneacetic acid;
  - 30 trans methyl (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanoate;
  - trans (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanoic acid;
  - 35 trans methyl (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanoate;
  - trans ethyl (3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzene acetate;

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trans (3R, 2S)-3-[4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]phenyl]-E-2-propenoic acid; and

trans N,N-diethyl-(3R, 2S)-4-[1-(4-fluorophenyl)-4-oxo-3-(3-phenylpropyl)-2-azetidiny]benzenepropanamide.

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6. A pharmaceutical composition comprising a cholesterol-lowering effective amount of a compound of any of claims 1, 2, 3, 4 or 5, alone or in combination with a cholesterol biosynthesis inhibitor, in a pharmaceutically acceptable carrier.

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7. The use of a compound of any of claims 1, 2, 3, 4 or 5 for the preparation of a medicament for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising a compound as defined in any of claims 1, 2, 3, 4 or 5, alone or in combination with a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier.

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8. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat or prevent atherosclerosis or to reduce plasma cholesterol levels which comprises in one container an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier, and in a second container, an effective amount of a compound of any of claims 1, 2, 3, 4 or 5 in a pharmaceutically acceptable carrier.

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9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of any of claims 1, 2, 3, 4 or 5, alone or in combination with a cholesterol biosynthesis inhibitor.

30

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/07117

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D205/08 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 524 595 (SCHERING CORPORATION) 27 January 1993 see claims & WO,A,93 02048 cited in the application ---	1-9
P,Y	WO,A,95 08532 (SCHERING CORPORATION) 30 March 1995 see claims -----	1-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
- \* "E" earlier document but published on or after the international filing date
- \* "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \* "O" document referring to an oral disclosure, use, exhibition or other means
- \* "P" document published prior to the international filing date but later than the priority date claimed

- \* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* "&" document member of the same patent family

Date of the actual completion of the international search

31 August 1995

Date of mailing of the international search report

6. 09. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040; Tx. 31-651 epo nl;  
Fax (+31-70) 340-3016

Authorized officer

Chouly, J

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/07117

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 9 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 95/07117

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-524595	27-01-93	AU-B- 658441	13-04-95
		AU-A- 2398092	23-02-93
		CA-A- 2114007	04-02-93
		CN-A- 1069024	17-02-93
		CZ-A- 9400142	13-07-94
		EP-A- 0596015	11-05-94
		HU-A- 67341	28-03-95
		JP-T- 6508637	29-09-94
		NO-A- 940221	21-01-94
		NZ-A- 243669	22-12-94
		QA-A- 9878	15-09-94
		WO-A- 9302048	04-02-93
		US-A- 5306817	26-04-94
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WO-A-9508532	30-03-95	AU-B- 7795294	10-04-95
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